American Journal of Hematology 59:110–114 (1998)

Progressive Expansion of Hypertensive Intracerebral Hemorrhage by Coagulopathy

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To test the hypothesis that an impaired coagulation system facilitates rapid expansion of hypertensive intracerebral hemorrhage (HICH), coagulation markers were assayed in plasma and their relations to both the hemorrhage size and its progressive expansion were analyzed. Ninety patients with HICH were studied. On admission, plasma samples were taken for the coagulation assay. Hematoma volume was calculated from a computed tomography (CT) scan and its enlargement was estimated by comparison to the volume of the hematoma calculated from a second CT scan taken later within 24 hr. Nine out of 90 patients showed enlargement in their hematoma size (enlarged hematoma group). Four of the enlarged hematoma group fell into acute fatal deterioration and died. Plasma levels of both fibrino peptide A (17.2 ± 7.8 vs. 4.0 ± 0.6 ng/ml, $P < 0.05$) and thrombin-antithrombin complex (21.9 ± 3.1 vs. 7.4 ± 2.8 ng/ml, not significant) were higher in the unchanged group than those in the enlarged hematoma group. In the hematoma-enlarged group fibrino-peptide A level did not exceed 10 ng/ml. In the hematoma unchanged group thrombin-AT-III complex values were positively correlated to hematoma volume. Thus, the coagulation system seemed to be highly activated depending on the hemorrhage volume within three hr after ictus in hypertensive intracerebral hemorrhage patients. When thrombin generation was not sufficient after bleeding, the hematoma seemed to be progressively enlarged. In conclusion, plasma levels of the coagulation markers on admission could be useful predictors of the possible enlargement of hematoma which leads to a poor outcome. Am. J. Hematol. 59:110–114, 1998. © 1998 Wiley-Liss, Inc.

Key words: hypertensive intracerebral hemorrhage; thrombin-antithrombin III complex (TAT); fibrino-peptide A

INTRODUCTION

In hypertensive intracerebral hemorrhage (HICH), bleeding is usually monophasic and lasts less than one hr [1–4]. In some patients, however, bleeding continues for a longer period [1,4–12] and causes the progressive enlargement of the hematoma, which results in a progressive neurological deterioration. To distinguish between such patients and patients with temporary bleeding on admission to the hospital is clinically important to prevent the ongoing damage and to improve the outcome. Though a variety of factors such as the location of bleeding, blood pressure, and vascular and coagulation disorders are reported to be related to the prolonged bleeding [1,10,13–15], the precise mechanism of prolonged bleeding in HICH and its predictors are not known. An impaired coagulation system apparently facilitates the progressive enlargement of hematoma. To investigate how the coagulation system plays a role in the extent of HICH formation, we assayed coagulation parameters such as soluble fibrin monomer (FM), thrombin–antithrombin-III complex (TAT) and fibrinopeptide A (FPA) in the systemic blood [16,17]. Using these parameters of thrombin

Contract grant sponsor: Ministry of Education, Science, and Culture, Japan; Contract grant numbers: 09670041 and 10670040; Contract grant sponsor: Ito Memorial Foundation; Contract grant sponsor: Smoking Research Foundation.

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Received for publication 29 August 1997; Accepted 13 May 1998

generation, we examined whether thrombin was adequately generated as a consequence of the activation of the coagulation system after bleeding. These parameters in HICH were higher than normal values and TAT levels were positively correlated with hematoma volume which was calculated from CT scans in the unchanged hematoma group. Those values of coagulation parameters in the enlarged hematoma group, however, were significantly lower than those of patients with temporary bleeding. In the enlarged hematoma group the coagulation system seemed not to be sufficiently activated after cerebral bleeding. We suggest that these parameters could be used as predictors of progressive hematoma enlargement in HICH.

MATERIALS AND METHODS

Patients With HICH

Ninety consecutive patients with HICH during a period of two years admitted to the department of neurosurgery of Seirei-Mikatahara hospital were studied. All the patients were admitted to the hospital within three hr after ictus.

Patients who had malignant diseases or bleeding tendency were omitted from the study. Patients were also excluded from this study if their CT scans, MRI, or cerebral angiograms revealed abnormalities such as definite aneurysm, arteriovenous malformation, moyamoya disease, cavernous angioma, venous angioma, or brain tumor. Patients under 16 years of age were omitted, and the mean age of the patients was 64.9 ± 12.1 (range from 47 to 90). Forty-three patients were men and 47 patients were women.

Liver dysfunction was defined as either elevated levels of both glutamic-transaminase (GOT) (>50 IU/L) and glutamic-pyruvic transaminase (GPT) (>50 IU/L) on admission or having a liver cirrhosis diagnosis before admission. The incidence of liver dysfunction was 33% (3/9) in the enlarged group and 6% (5/81) in the unchanged group, which were significantly different ($P < 0.05$). Diabetes Mellitus (DM) and hypertension (HT) were defined from their disease histories. The incidence of DM was 0% (0/9) in the enlarged group and 6% (5/81) in the unchanged group, and those with HT were 56% (5/9) and 56% (45/81), respectively. These values were not significantly different. Uncontrolled HT was defined as continuous high systolic blood pressure (>180 mmHg) for 24 hr. Its incidence was 22% in both groups (2/9 vs. 18/81). Thrombocytopenia was defined as a platelet count below $12 \times 10^4/\mu l$ on admission. The incidence of thrombocytopenia was 11% (1/9) in the enlarged group and was 9% (7/81) in the unchanged group, which were not significantly different.

Estimation of Hematoma Volume From CT Scan

The hematoma volume was estimated by a simplified method [15] from CT scans on admission. Briefly, the cubic content of the hematoma was calculated from maximum width (X), length (Y), and height (Z), as seen on the CT scans; the three dimensions (X, Y, and Z) were multiplied together, and half of that value ($X \times Y \times Z \times \pi/6 = X \times Y \times Z/2$: $P = 3$) was taken as the hematoma volume. Hemorrhage within the ventricular system was not measured. All the patients received the second CT scans within 24 hr after ictus.

Assay of Coagulation Parameters

Blood samples were collected on admission (within three hr after ictus) by vein puncture from the antecubital vein by a well-trained neurosurgeon. We measured plasma levels of TAT, FPA, and FM. Other routine laboratory tests for the coagulation system, such as prothrombin time, platelets count, and fibrinogen level were also measured.

TAT and FPA were measured by use of enzyme-linked immunosorbent assay (ELISA) (TAT: Enzygnost, Hoechst Japan Co., Tokyo, Japan; FPA: Asserachrom FPA, Boehringer Mannheim Co., Tokyo, Japan), and FM was measured by use of a rapid agglutination tests (FM Test, Boehringer Mannheim Co., Tokyo, Japan).

Analysis

The correlation between hematoma volume and plasma levels of these coagulation parameters was analyzed. We also compared the levels of the coagulation parameters between the two subgroups of the enlarged hematoma group and the unchanged hematoma group. Statistical analyses were performed by one-way analysis of variance (ANOVA). A *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Incidence of Hematoma Enlargement

Nine out of 90 patients (10%) showed enlargement of the cerebral hematoma in the second CT scan compared with the first CT scan and were categorized as the ''enlarged hematoma group''; the other 81 (90%), showed stable hematoma and were categorized as the ''unchanged hematoma group.'' Of the nine patients in the enlarged hematoma group, seven patients were men and two were women; eight of nine (89%) had putaminal hemorrhage and the other had a hemorrhage in the thalamus. Four of nine (44%) fell into acute fatal deterioration and died. None of the enlarged hematoma group had a history of a bleeding tendency. Of the 81 patients in the unchanged hematoma group, 12 out of the 81 (15%) died and of the 12 that died, six had a pontine hemorrhage and

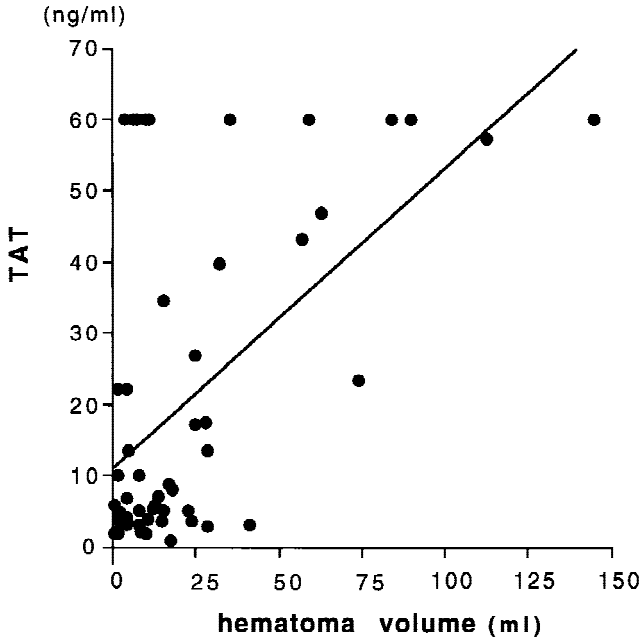

Fig. 1. Relationship between plasma TAT level and hematoma volume on admission in the unchanged hematoma group. Significant positive correlation (R = 0.48, *P* = 0.0001) was observed between these two values in the unchanged hematoma group.

the others had a hemorrhage in one of the following: putamen, thalamus, subcortex, or cerebellum.

Relationship Between Hematoma Volume and Coagulation Parameters

The hematoma volume of the patients in the enlarged hematoma group on admission was 40.9 ± 7.8 ml (mean ± SD), which was significantly larger than that of the unchanged hematoma group (20.7 ± 3.3 ml, $P = 0.049$, $F = 4.00$) (Fig. 1).

Prothrombin time (enlarged group: 104.1 ± 8.9% vs. unchanged group: 113 ± 22%), plasma fibrinogen level (280 ± 96 vs. 211 ± 116 mg/dl), and platelets count (19.6 ± 7.7 vs. 16.7 ± 12.4 × $10^4/\mu l$) were not significantly different between the two groups.

Plasma FPA levels of the unchanged hematoma group on admission was 17.2 ± 2.8 ng/ml (Table 1), which was far higher than the normal range (<2.0 ng/ml). There was no significant correlation between hematoma volume and plasma FPA levels in the unchanged hematoma group (Data not shown).

The mean plasma FPA level in the enlarged hematoma group was 4.0 ± 0.6 ng/ml, which was significantly lower than that of the unchanged hematoma group ($P = 0.047$, $F = 4.19$, Table 1). In all the patients of the enlarged group, plasma FPA level was below 10.0 ng/ml.

Plasma TAT levels of the unchanged hematoma group on admission was 21.9 ± 3.1 ng/ml, which was far higher than the normal range (<3.0 ng/ml) (Table 1). The elevated plasma TAT levels decreased to 8.2 ± 1.5 ng/ml on the day after ictus. There was a significant correlation between hematoma volume and plasma TAT levels in the unchanged hematoma group ($P < 0.0001$, Fig. 1). Plasma TAT levels in the patients of the enlarged hematoma group was 7.4 ± 2.8 ng/ml, which tended to be lower than that of the unchanged hematoma group, and did not show significant correlation with hematoma volume (Table 1).

TABLE I. Difference in Hematoma Volume and Plasma Levels of FPA and TAT on Admission Between the Unchanged Hematoma Group and the Enlarged Hematoma Group*

Parameters	Enlarged group	Unchanged group	*P* value
Hematoma volume (ml)	40.9 ± 7.8	20.7 ± 3.3	$P < 0.05$
FPA (ng/ml)	4.0 ± 0.6	17.2 ± 2.8	$P < 0.05$
TAT (ng /ml)	7.4 ± 2.8	21.9 ± 3.1	NS
TAT (volume matched)	7.4 ± 2.8	31.2 ± 4.9	$P < 0.05$

*FPA, fibrinopeptide A; TAT, thrombin–antithrombin-III complex. Hematoma volume was calculated from CT scan on admission as described in Materials and Methods. Volume-matched TAT indicates plasma TAT levels of unchanged hematoma patients with hematoma larger than 10 ml (41/81) and those of the enlarged hematoma group (9/9). These values were compared to exclude the influence of hematoma size. Data are shown as mean ± SD.

To exclude the possibility that the significant difference of TAT levels was caused by a difference in hematoma volume, we compared plasma TAT levels of the enlarged hematoma group with those of the unchanged hematoma group whose hematoma volume was larger than 10 ml (41 out of 81 patients, 54%). TAT level in these 41 patients was 31.2 ± 4.9 ng/ml, which was significantly higher than that of the enlarged hematoma group ($P = 0.011$, $F = 7.48$, Table 1).

Because the fibrin monomer test is required to be performed quickly after sample collection without freezing, the test was conducted on the patients ($N = 22$) only when a skillful technician was available at bedside. Results of the fibrin monomer tests of the enlarged hematoma group were all negative ($N = 6$). However, in four out of the 16 (25%) in the unchanged hematoma group which were tested, soluble fibrin monomer was positively detected in the plasma.

DISCUSSION

To establish the possible involvement of impaired coagulation activity in the development of enlarged hematoma in HICH, we measured levels of TAT and FPA in the patients' plasma on admission. We found that in HICH patients, the coagulation system was highly activated within three hr after ictus. The amounts of generated thrombin correlated well to the hematoma volume in the unchanged hematoma group, suggesting that adequate amount of thrombin was generated to stop bleed-

ing. The amounts of thrombin generated in the enlarged hematoma group, however, seemed to be insufficient to stop bleeding which results in the progressive expansion of the hematoma.

Because liver dysfunction was often found in hematoma enlargement patients in HICH, suppression of either the coagulation system or platelet aggregation has been suggested to be directly related to the prolonged bleeding in HICH [18–20]. Both FPA and TAT are direct indicators of thrombin generation in plasma, and well reflect the amounts of generated thrombin. FPA is released from fibrinogen after cleavage of Aα chain by thrombin [16]. TAT is a rapidly inactivated and a complex form of thrombin by ATIII in plasma [17]. High levels of these parameters in HICH suggest that the coagulation pathways are activated after bleeding. The brain contains high concentrations of tissue factor that, if released into the circulation or exposed to the blood stream after intracerebral hemorrhage, activates the extrinsic coagulation pathway [21–26] to stop bleeding. Increases in TAT and FPA levels in HICH, therefore, were likely initiated by the activation of the extrinsic coagulation pathway.

A positive correlation between TAT and hematoma volume in the unchanged hematoma group suggests that larger amounts of thrombin were generated to stop larger amounts of bleeding. In the unchanged hematoma group there seemed to be a mechanism to stop bleeding by the generation of adequate amounts of thrombin. The coagulation system, therefore, seems to be well controlled to be activated at the lesion for a period required for cessation of bleeding.

The plasma levels of FPA in the enlarged hematoma group were significantly lower than those in the unchanged hematoma group although the average of the hematoma volume was significantly higher in the former group. The plasma levels of TAT in the enlarged hematoma group also tended to be lower than those in the unchanged hematoma group. When their hematoma volumes were matched (more than 10 ml), the plasma TAT levels in the enlarged hematoma group were significantly lower than those in the unchanged hematoma group. These results suggest that thrombin generation after bleeding was not enough to stop bleeding successfully in the hematoma enlarged group, which resulted in the prolonged bleeding. Together with other risk factors such as sustained hypertension, insufficient thrombin generation seems to play a role in the hematoma enlargement.

It is difficult at this moment to speculate as to why sufficient amounts of thrombin were not generated in the enlarged hematoma group after bleeding. In this study we found that it may be possible to predict the progressive hematoma enlargement in HICH patients early, on admission, by measurement of these parameters. For example, when plasma TAT and FPA levels on admission were relatively low compared with their hematoma volume, progressive enlargement of hematoma could be suggested at a high rate. A level of 10 ng/ml of FPA could be a marking point, since all the patients in the enlarged hematoma group showed less than 10 ng/ml of FPA levels. Soluble fibrin monomer, which can be assayed quickly by a rapid agglutination test, could be another possible predictor.

In conclusion, patients with hematoma enlargement in HICH had lower coagulation activity. Such a low response of the coagulation system in response to bleeding could be diagnosed by plasma TAT and FPA levels on admission.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for Scientific Research, nos. 09670041 and 10670040 from the Ministry of Education, Science, and Culture, Japan; a grant from Ito Memorial Foundation; and the Smoking Research Foundation Grant for Biomedical Research.

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